

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently amended) A method for the analysis of methylation patterns comprising the following steps:

- (a) isolation of genomic nucleic acids from a biological sample,
- (b) amplification of one or more target nucleic acids of said genomic nucleic acids in a manner whereby the methylation patterns of said genomic nucleic acids are maintained in the amplified nucleic acid,
- (c) performing mass spectrometry on said amplified nucleic acid or fragments thereof to obtain mass spectra₁,
- (d) evaluating the obtained mass spectra₁ and
- (e) determining the methylation pattern and/or methylation status of the sample.

2. (Original) A method according to claim 1, characterised in that in step a) the genomic DNA is obtained from cells or cellular components which contain DNA, sources of DNA comprising, for example, cell lines, biopsies, blood, sputum, stool, urine, cerebral-spinal fluid, tissue embedded in paraffin such as tissue from eyes, intestine, kidney, brain, heart, prostate, lung, breast or liver, histological object slides, and all possible combinations thereof.

3. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, characterised in that step b) is carried out by means of the following additional steps or sub-steps:

- (i) amplification of the target genomic nucleic acid sequence in a semiconservative manner,

(ii) methylation of the synthesized strand whereby the 5' cytosine methylation status of the CG dinucleotides in the template strand is copied to the CG dinucleotides of the synthesized strand.

4. (Original) A method according to claim 3, characterised in that it is further comprising the following steps:

iii) denaturation of the double stranded nucleic acids to form single stranded nucleic acids,

iv) repetition of steps i) to iii) until a desired number of amplicates is obtained.

5. (Currently amended) A method according to ~~claims~~ claim 3 ~~or 4~~, wherein in step i) the method of amplification is selected from: ligase chain reaction, polymerase chain reaction, polymerase reaction, rolling circle replication.

6. (Currently amended) A method according to ~~claims~~ claim 3 ~~or 4~~, wherein in step ii) said methylation is carried out by enzymatic means.

7. (Original) A method according to claim 6 wherein said enzyme is a maintenance methyltransferase.

8. (Currently amended) A method according to ~~one of claims~~ claim 6 ~~or 7~~, wherein the methyltransferase is DNA (cytosine-5) Methyltransferase (DNMT 1).

9. (Currently amended) A method according to ~~one of claims~~ claim 6 ~~to 8~~, wherein the methyl group is obtained from the donor molecule S-adenosylmethionine.

10. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein step b) is carried out by means of the following additional steps or sub-steps

(1) heating the genomic DNA to a temperature operative to cause denaturation,

(2) cooling the denatured DNA in the presence of single stranded oligonucleotide primers such that the primers anneal to the DNA,

(3) heating the mixture in the presence of a polymerase and nucleotides to a temperature such that the primers are extended,

(4) contacting the double stranded nucleic acid with enzymes and/or agents under conditions conducive to the methylation of the synthesised strand such that the CpG dinucleotides within the synthesised strand are methylated according to the methylation status of the corresponding CpG dinucleotide on the template strand thereby preserving the genomic methylation pattern,

(5) repeating steps (1) to (4) a desired number of times to reach a desired number of nucleic acids.

11. (Currently amended) A method according to ~~one of the claim 1 to 10~~, wherein the amplify nucleic acids are fragmented prior to step C.

12. (Original) A method according to claim 11, wherein said fragmentation is carried out by enzymatic or chemical means.

13. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein step c) is carried out by means of time-of-flight MALDI or ESI mass spectrometry.

14. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein in step c) internal and/or external calibration is used.

15. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein, prior to step c) the nucleic acids are purified.

16. (Original) A method according to Claim 15, wherein said nucleic acids are single stranded.

17. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein the amplificate nucleic acids are less than 100 base pairs in length.

18. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein any primer oligonucleotides used during step b) do not contain CG dinucleotides.

19. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein said amplicates are immobilised upon a solid phase.

20. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein the synthesised amplicates comprise at least one chemical modification of an internucleoside linkage, a sugar backbone, or a nucleoside base.

21. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, characterised in that steps d) and e) are carried out as follows:

d) comparing the obtained mass spectra with reference mass spectra obtained of the nucleic acid in its fully methylated and/or fully unmethylated form and

e) determining by said comparison whether fragments are methylated, unmethylated or partially methylated and thereby determining the methylation pattern of the nucleic acid.

22. (Currently amended) A method according to ~~one of the claims~~ claim 1 to 20 characterised in that steps d) and e) are carried out as follows:

d) determining the molecular weight of the fragment or fragments

e) determining the methylation status of said fragments.

23. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein the methyl group carries a detectable label which is incorporated into the synthesised nucleic acid strand.

24. (Currently amended) A method according to ~~one of the preceding claims~~ claim 1, wherein a mass label is incorporated into the amplificate nucleic acids.

25. (Currently amended) The use of a method according to ~~Claims~~ claim 1 ~~to 24~~ for the analysis of methylation patterns within genomic DNA.

26. (Currently amended) A kit for analysis of methylation within nucleic acids according to any one of Claims 1 to 25 comprising

- reagents for the methylation retaining amplification of genomic DNA,
- reagents for the mass spectrometric analysis of nucleic acids.